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(54) Title: HYDROXYPROPYLCELLULOSE AND ANIONIC POLYMER COMPOSITIONS AND THEIR USE AS PHARMACEUTICAL FILM COATINGS

(57) Abstract

A composition comprising hydroxypropylcellulose and at least one anionic polymer, such as sodium carboxymethylcellulose and the use of aqueous solutions thereof for coating substrates such as tablets, granules, beads, etc.

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HYDROXYPROPYLCELLULOSE AND ANIONIC POLYMER COMPOSITIONS AND THEIR USE AS PHARMACEUTICAL FILM COATINGS

Field of the Invention

The present invention relates to film forming compositions and more particularly it relates to compositions comprising hydroxypropylcellulose and sodium carboxymethylcellulose.

Background of the Invention

Coating tablets, granules and beads with polymeric film forming compositions is well known in the pharmaceutical industry. In addition to pharmaceutical books, manuals and technical literature, patent publications in this field include: U.S. Patent No. 4,931, 286 disclosing high gloss pharmaceutical tablet which comprises an active ingredient in a binder matrix as a core with an outermost coating of sodium carboxymethylcellulose (SCMC) having a degree of substitution (DS) of 0.2-14 and a degree of polymerization (DP) of 150-400 and a polyethylene glycol (PEG) plasticizer. The outermost coating is applied from a water solution by spray coating. The tablet has a much higher gloss than other cellulosic polymers. This eliminates the need to increase the gloss by an additional coating. In addition, only very small amounts of sodium carboxymethylcellulose are needed, thus providing an unexpected economic advantage in terms of raw material costs and processing times. Further, sodium carboxymethylcellulose films dissolve much more rapidly than films e.g. hydroxypropymethyl cellulose and so are less likely to interfere with the dissolution of drug from a coated tablet.

Hydroxypropylcellulose has been used very successfully in aqueous film coatings to enhance the utility of hydroxypropylmethylcellulose (The Use of Klucel hydroxy-propylcellulose (HPC), NF, to increase the Utility of hydroxypropylmethylcellulose (HPMC) in Aqueous Film Coating, Aqualon Technical Bulletin VC-556A). Hydroxypropylmethylcellulose has high tensile strength and a very low percent elongation. When Klucel HPC, with its high percent elongation, is

added to the traditional hydroxypropylmethylcellulose film coating, the film flexibility and substrate adherence is greatly increased.

U.S. Patent No. 4,316,884 discloses that indoprofen can be used in increased safety at its effective anti-inflammatory dose in humans and that the activity of indoprofen is greatly prolonged by micro encapsulating micro particles of indoprofen in a solid protective coating of a cellulose ether such as ethylcellulose.

Summary of the Invention

According to the present invention there is provided a composition comprising hydroxypropylcellulose and at least one anionic polymer e.g. carboxymethyl ether salts of cellulose, methacrylic acid polymers and copolymers, carboxyvinyl polymers and copolymers, alginic acid salts, pectinic acid salts, pectic acid salts, carrageenan, agar and carboxylic acid salts of polysaccharides.

Further provided is a composition comprising a substrate and a coating comprising hydroxypropylcellulose and at least one anionic polymer.

Still further provided is a process for coating a substrate comprising (a) preparing an aqueous solution of hydroxypropylcellulose and anionic polymer and (b) applying said solution to the substrate.

As used herein the term "consisting essentially of" means that the named ingredients are essential, however, other ingredients which do not prevent the advantages of the present invention from being realized can also be included.

Detailed Description of the Invention

It has been found that compositions of hydroxypropylcellulose and anionic polymer, such as sodium carboxymethylcellulose, have film-forming characteristics. Films of these compositions show good tensile strength and percent elongation as well as provide high gloss film coatings.

Anionic polymers suitable for use in the present invention are carboxymethyl ether salts of cellulose, preferably SCMC, methacrylic acid polymers and copolymers, carboxyvinyl polymers and copolymers, alginic acid salts , pectinic acid salts, pectic acid salts, carrageenan, agar and carboxylic acid salts of polysaccharides.

Sodium carboxymethyl cellulose suitable for use in the present invention has a degree of substitution (DS) of at least 0.2 and preferably at least about 0.5. The degree of substitution of the sodium carboxymethyl cellulose can be up to about 2.5, preferably up to about 0.9. The degree of polymerization (DP) of the sodium carboxymethylcellulose is at least about 100, preferably at least about 200. The sodium carboxymethylcellulose degree of polymerization can be up to about 4,000, preferably up to about 1,000.

Hydroxypropylcellulose suitable for the present invention has a weight average molecular weight of at least about 80,000. The molecular weight of the hydroxypropylcellulose can be up to about 1,150,000, preferably up to about 95,000.

The degree of substitution for the sodium carboxymethyl cellulose is given by carboxymethyl groups based on 3.0 as total substitution of available androhexoic sites. Sodium carboxymethylcellulose is a cellulose gum available as Aqualon® SCMC from Hercules Incorporated. As a 99.5% purity free flowing powder it meets all specifications of the US PHARMACOPEIA.

Hydroxypropylcellulose is a cellulose gum available as Klucel® hydroxypropylcellulose from Hercules Incorporated. As a free flowing powder it meets all specifications of the US PHARMACOPEIA.

The weight ratio of hydroxypropylcellulose to sodium carboxymethylcellulose is at least about 1:20, preferably at least about 1:4. The hydroxypropylcellulose:sodium carboxymethylcellulose weight ratio can be up to about 20:1, preferably up to about 4:1.

Optionally, plasticizer can also be present in the composition of the present invention. Suitable plasticizers are ethanolamines, ethylene glycol, glycerol, 1,2,6-hexanetriol, mono-, di-, and triacetin, 1,5-pentanediol, sorbitol, polyethylene glycol (weight average molecular weight up to about 600), propylene glycol and trimethylolpropane. The preferred plasticizer is polyethylene glycol, preferably having a molecular weight of about 400. When present, the plasticizer is at least one percent by weight based on the total composition, preferably at least about 5.5 percent by weight. The plasticizer, when present, can be up to about 50% by weight, preferably up to about 20 percent by weight based on the total composition.

The composition of the present invention is particularly suitable for use as a coating on substrates e.g. for the coating of tablets, granules, beads etc. One

specific area of use is for the coating of pharmaceutical substrates e.g. tablets containing pharmaceutically active ingredients, or may be applicable for novel pharmaceutic dosage forms. In this type of application pharmaceutically approved plasticizer, such as polyethylene glycol can be used.

Other ingredients can also be incorporated in the coating composition, such as active pharmaceutical ingredients, active cosmetic ingredients, nutritional supplements, colorants, opacifying materials, surfactants, stabilizers, silicas, silicones, preservatives, surface treatment agents, flavorants, crosslinking agents, and other polymers deemed necessary and useful in promoting the utility, value and ease of preparation or coating of the tablets, granules, beads and other novel pharmaceutical dosage forms.

Representative types of active medicaments include antacids, anti-inflammatory substances, (including but not limited to non-steroidal anti-inflammatory drugs, NSAIDs, vasodilators, coronary vasodilators, cerebral vasodilators, and perpheral vasodilators), anti-infectives, phsychotropics, antimanics, stimulants, antihistamines, laxatives, decongestants, vitamines, gastrointestinal sedatives, antidiarrheal preparations, antianginal drugs, antiarrhythmics, antihypertensive drugs, vasoconstrictors and migraine treatments, anticoagulants and anti-thrombotic drugs, analgesics, anti-pyretics, hypnotics, sedatives, antiemetics, anti-nauseants, anticonvulsants, neuromuscular drugs, hyper-and hypoglycemic agents, thyroid and antithyroid preparations, diuretics, antispasmodics, uterine relaxants, mineral and nutritional additives, anti-obesity drugs, anabolic drugs, erythropoietic drugs, antiasthmatics, expectorants, cough suppressants, mucolytics, antiuricemic drugs, and other drugs or substances acting locally in the mouth, such as topical analgesics, local anesthetics, polypeptide drugs, anti-HIV drugs, chemotherapeutic and antineoplastic drugs etc.

Examples of specific active medicaments include aluminum hydroxide, prednisolone, dexamethasone, aspirin, acetaminophen, ibuprofen, isosorbide dinitrate, nicotinic acid, tetracycline, ampicillin, dexbrompheniramine, chlorpheniramine, albuterol pseudophedrine, loratadine theophylline, ascorbic acid, tocopherol, pyridoxine, methoclopramide, magnesium hydroxide, verapamil, procainamide hydrochloride, propranolol, captopril, ergotamine, flurazepam, diazepam, lithium carbonate, insulin, furosemide, hydrochlorothiazide, guaiphenesin,

dextromethorphan and benzocaine, although any active medicament which is physically and chemically compatible with the hydroxypropyl cellulose and anionic polymer blend and other tablet ingredients.

Formulations containing NSAIDs (including for the purposes of this application acetaminophen) may also contain therapeutic amounts of other pharmaceutical actives conventionally employed with NSAID including but not limited to decongestants or bronchodilators (such as pseudoephedrine, phenylpropanolamine, phenylephrine and pharmaceutically acceptable salts thereof), antitussives (such as caraminophen, dextromethorphan and pharmaceutically acceptable salts thereof), antihistamines (such as chlorpheniramine, brompheniramine, dexchlorpheniramine, dexbrompheniramine, triprolidine, doxylamine, tripelennamine, cyproheptadine, pyrilamine, hydroxyzine, promethazine, azatadine and pharmaceutically accptable salts thereof), non-sedating antihistamines (such as acrivastine, astemizole, cetirizine, ketotifen, loratidine, temelastine, terfenadine (including the metabolites disclosed in U.S. Pat. Nos. 4,254,129 and 4,285,957 hereby incorporated by reference and pharmaceutically acceptable salts thereof), muscle relaxants (such as glycerylmonether SMRs, methocarbamol, mephenesin, mephenesin carbamate, cyclobenzaprine, chlorzoxazone, mephenesin acid succinate, chlorphenesin carbamate, or pharmaceutically acceptable salts thereof) and adjuvants (such as diphenhydramine, caffeine, xanthine derivatives (including those disclosed in U.S. Pat. No. 4,558,051, hereby incorporated by reference) and pharmaceutically acceptable salts thereof, nutritional supplements and combinations of any of the aforesaid pharmaceuticals. The aforesaid pharmaceuticals may be combined with acetaminophen for the treatment of allergies, cough, colds, cold-like and/or flu symptoms in mammals including humans. However, these pharamaceuticals maybe combined with acetaminophen as sleep aids (such as diphenhydramine), or for other known purposes.

Anionic polymers, such as sodium carboxymethyl cellulose cross-link in the presence of certain polyvalent cations. Sodium carboxymethylcellulose (SCMC) is an anionic water-soluble polymer. The chemical and physical properties of SCMC make it useful in a wide range of applications, such as food, pharmaceuticals and personal care. Treatment of aqueous solutions of SCMC with certain polyvalent salts results in its precipitation. However, the gradual release of polyvalent cations,

such as Al^{+3}, to SCMC solutions leads to uniform cross-linking of the polymer molecules through carboxymethyl groups. This produces a gel. The nature of the gel depends in turn, on the amount of cross-linking agent present, the concentration and the DP of the polymer molecules. The rate at which gelation occurs depends upon how quickly the Al^{+3} ions are allowed to dissociate into the aqueous system. The ultimate qualities of the gel and gelling times can be controlled by varying the viscosity grade and amount of SCMC used, the proportion of a polyvalent cation and the pH of the medium.

The active ingredients that can be incorporated in the coating composition and in the substrate (e.g. tablets, granules, beads etc.) can be pharmaceutically active ingredients such as hypnotics, sedatives, antiepileptics, awakening agents, psychoneurotropic agents, neuromuscular blocking agents, antispasmodic agents, antihistaminics, antiallergics, cardiotonics, antiarrhythmics, diuretics, hypotensives, vasopressors, antitussive expectorants, thyroid hormones, sexual hormones, antidiabetics, antitumor agents, antibiotics, chemotherapeutics, and narcotics.

The coating composition and the substrate (e.g. tablets, granules, beads etc.) may contain cosmetically active agents such as breath freshening compounds like menthol, other flavors and fragrances commonly used for oral hygiene, and for dental and oral cleansing like quaternary ammonium bases. The effect of flavors may be enhanced using flavor enhancers like tartaric acid, citric acid, vanillin, or the like.

The composition of the present invention is preferably applied from aqueous solution for the coating of substrates such as tablets.

The preferred process for coating the substrate with the composition of the present invention comprises preparing an aqueous solution of hydroxypropylcellulose and anionic polymer, e.g. sodium carboxymethylcellulose and applying the aqueous solution to the substrate. Optionally, plasticizer as indicated above can also be present in the coating composition. In making the aqueous solution of sodium carboxymethylcellulose, hydroxypropylcellulose and plasticizer, the solutions can be made up together or alternatively can be made up separately. Suitable coating weight will preferably be at least about 0.5%, more preferably at least about 0.75% by weight based on the total weight of the coated

substrate. The coating weight can be up to about 10% by weight preferably up to about 2% by weight of the total coated composition.

High gloss pharmaceutical tablets generally comprise at least one pharmaceutically active ingredient in a binder matrix core having a coating of anionic polymer, e.g., sodium carboxymethylcellulose, hydroxypropylcellulose and optionally a plasticizer.

The composition of the present invention has industrial applicability in the manufacturing of pharmaceutical formulations.

The following examples are given for the purpose of illustration only and are not intended to limit the scope of the present invention. All parts and percentages are by weight unless otherwise indicated.

EXAMPLE 1

In this example, an air suspension column coater, Glatt GPCG5/9, available from Glatt Air Techniques was set up as follows:

Spray Gun:	Port size, mm	1.2
	Spacer ring, mm	3.0
	Atomization air pressure, bar	1.8
Pump, Peristaltic		
	Delivery rates, g/min	28
Column		
	Inlet air damper setting	open
	Outlet air damper setting, %	45
	Batch size, kg	3
	Inlet air temperature, °C	60
	Outlet air temperature, °C	48

The tablets are pneumatically fluidized through a cylindrical coating partition past a spray nozzle which is mounted in the center of the bottom orifice plate of the product chamber. As the tablets pass through the spray they are coated with the aqueous solution. The region outside the partition is the down bed. The air flow in this region keeps the tablets in near weightless suspension so that they can move rapidly downward and can be drawn horizontally in to the gap at the base of the

coating partition. This process continues until the tablets have achieved the desired coating.

With stirring, 24.8 g of sodium carboxymethyl cellulose, available from Hercules Inc. as Aqualon® 7L2P CMC; and 24.8 g of hydroxypropylcellulose, available from Hercules Inc. as Klucel® EF hydroxypropylcellulose, was mixed with 906.5 g of deionized water. Mixing was continued until the solution cleared. Then 7.7 g of polyethylene glycol, available from Union Carbide as PEG 400, was added to the solution and mixed until a uniform solution was obtained. Solution viscosity was measured to obtain a value between 125 and 300 cps in order to provide good coating using the Glatt GPCG-5 coater.

Two kg of biconvex placebo tablets were charged to the fluid bed and allowed to warm up for five minutes. The coating solution was then applied to the tablets. The weight gain was 1.9%. The disintegration time of these tablets was 4:00 minutes. The gloss of these tablets was higher than those obtained with hydroxypropyl-cellulose/hydroxypropylmethylcellulose coating.

Gloss was measured on a Multi Angular Reflectometer ASTM D523-89

Gloss			
	20°	60°	80.5°
HPC/HPMC 1/1	13.7	30.9	43.1
HPC/CMC 1/1	8.1	26.9	51.2
HPC/CMC 2/1	15.0	54.2	90.8
HPC/CMC 1/2	36.3	68.8	89.3
8.7% PEG 400, based on polymer weight			

Example 2

With stirring 24.8 g of Aqualon® 7L2P sodium carboxymethyl cellulose was added to 595.2 g of deionized water, and 24.8 g of Klucel® EF hydroxypropylcellulose was mixed with 235.2 g of deionized water. Mixing was continued until the solution cleared. Then 3.9 g of polyethylene glycol, available from Union Carbide as PEG 400, was added to both solutions and mixed until uniform solutions were obtained. 3.1 g of aluminum chloride was dissolved in 50 g of deionized water. This solution was added to the hydroxypropylcellulose solution and

mixed until a uniform solution was obtained. Solution viscosity was measured to obtain a value between 125 and 175 cps in order to provide good coating using the Glatt GPCG-5 were charged to the fluid bed and allowed to warm up for five minutes. The spraying was begun with a layer of sodium carboxymethyl cellulose followed by a layer of hydroxypropylcellulose. These layers were alternated and the final layer was sodium carboxymethyl cellulose. The weight gain was 1.7%.

The disintegration time of the layered tablets was 8:10 minutes.

Claims:

1. An aqueous coating composition providing high gloss coatings consisting essentially of hydroxypropyl cellulose and at least one anionic polymer.

2. The composition of claim 1 wherein the anionic polymer is selected from the group consisting of carboxymethyl ether salts of cellulose, methacrylic acid polymers and copymers, carboxyvinyl polymers and copolymers, alginic acid salts, pectinic acid salts, pectic acid salts, carrageenan, agar and carboxylic acid salts of polyaccharides.

3. The composition of claim 2 wherein the anionic polymer is selected from the group consisting of carboxymethyl ether salts of cellulose.

4. The composition of claim 3 wherein the carboxymethyl ether salt of cellulose is sodium carboxymethylcellulose.

5. The composition of claim 4 wherein the sodium carboxymethylcellulose has a degree of substitution of at least about 0.2.

6. The composition of claim 4 wherein the sodium carboxymethylcellulose has a degree of substitution of up to about 2.5.

7. The composition of claim 4 wherein the sodium carboxymethylcellulose has a degree of polymerization of at least about 100.

8. The composition of claim 4 wherein the sodium carboxymethylcellulose has a degree of polymerization of up to about 4,000.

9. The composition of claim 2 wherein the hydroxypropylcellulose has a molecular weight of at least about 80,000.

10. The composition of claim 2 wherein the hydroxypropylcellulose has a molecular weight of up to about 1,150,000.,

11. The composition of claim 2 comprising a plasticizer.

12. The composition of claim 4 wh rein the weight ratio of hydroxypropylcellulose:sodium carboxymethylcellulose is at least about 1:20.

13. The composition of claim 4 wherein the weight ratio of hydroxypropylcellulose:sodium carboxymethylcellulose is up to about 20:1.

14. The composition of claim 11 wherein the amount of plasticizer is at least about 1% by weight based on the total composition.

15. The composition of claim 11 wherein the amount of plasticizer is up to about 50% by weight based on the total composition.

16. The composition of claim 2 containing at least one additive selected from the group consisting of cross-linking agents, pharmaceutically active ingredients, cosmetically active ingredients and nutritional supplements.

17. The composition of claim 4 wherein the sodium carboxymethylcellulose has a degree of substitution of from about 0.2 to about 2.5 and a degree of polymerization of from about 100 to about 4,000, the hydroxypropylcellulose has a weight average molecular weight of from about 80,000 to about 1,150,00, the weight ratio of hydroxypropylcellulose:sodium carboxymethylcellulose is from about 1:20 to about 20:1 and optionally comprising additive selected from the group consisting of plasticizer, cross-linking agents, pharmaceutically active ingredients, cosmetically active ingredients and nutritional supplements.

18. The composition of claim 17 wherein the sodium carboxymethylcellulose has a degree of substitution of at least about 0.5.

19. The composition of claim 17 wherein the sodium carboxymethylcellulose has a degree of substitution of up to about 0.9.

20. The composition of claim 17 wherein the sodium carboxymethylcellulose has a degree of polymerization of at least about 200.

21. The composition of claim 17 wherein the sodium carboxymethylcellulose has a degree of polymerization of up to about 1,000.

22. The composition of claim 17 wherein the hydroxypropylcellulose has a molecular weight of at least about 80,000.

23. The composition of claim 17 wherein the hydroxypropylcellulose has a molecular weight of up to about 95,000.

24. The composition of claim 17 comprising a plasticizer selected from the group consisting of polyethylene glycol ethanolamines, ethylene glycol, glycerol, 1,2,6-hexanetriol, mono-, di-, and triacetin, 1,5-pentanediol, sorbitol, polyethylene glycol, propylene and glycol trimethylolpropane.

25. The composition of claim 17 wherein the weight ratio of hydroxypropylcellulose:sodium carboxymethylcellulose is at least about 1:4.

26. The composition of claim 17 wherein the weight ratio of hydroxy-propylcellulose:sodium carboxymethylcellulose is up to about 4:1.

27. The composition of claim 17 wherein the amount of plasticizer is at least about 5.5% by weight based on the total composition.

28. The composition of claim 17 wherein the amount of plasticizer is up to about 20% by weight base do the total composition.

29. The composition of claim 17 wherein the sodium carboxymethylcellulose has a degree of substitution of from about 0.5 to about 0.9 and a degree of polymerization of from about 200 to about 1,000, the hydroxypropylcellulose has a weight average molecular weight of from about 80,000 to about 95,000, the weight ratio of hydroxypropylcellulose:sodium carboxymethylcellulose is from about 1:4 to about 4:1, and optionally comprising additive selected from the group consisting of cross-linking agents, pharmaceutically active ingredients, cosmetically active ingredients, nutritional supplements and plasticizer selected from the group consisting of ethanolamines, ethylene glycol, glycerol, 1,2,6-hexanetriol, mono-, di-, and triacetin, 1,5-pentanediol, sorbitol, polyethylene glycol, propylene and glycol trimethylolpropane.

30. The composition of claim 17 wherein the plasticizer is polyethylene glycol.

31. The composition of claim 28 wherein the polyethylene glycol has a molecular weight of about 400.

32. A composition comprising a substrate and a coating comprising the composition of claim 1.

33. A composition comprising a substrate and a coating comprising the composition of claim 2.

34. A composition comprising a substrate and a coating comprising the composition of claim 4.

35. A composition comprising a substrate and a coating comprising the composition of claim 17.

36. A composition comprising a substrate and a coating comprising the composition of claim 29.

37. The composition of claim 32 wherein the substrate comprises pharmaceutically active ingredients.

38. The composition of claim 33 wherein the substrate comprises pharmaceutically active ingredients.

39. The composition of claim 34 wherein the substrate comprises pharmaceutically active ingredients.

40. The composition of claim 35 wherein the substrate comprises pharmaceutically active ingredients.

41. The composition of claim 36 wherein the substrate comprises pharmaceutically active ingredients.

42. The composition of claim 32 wherein the pharmaceutically active ingredients are selected from the group consisting of hypnotics, sedatives, antiepileptics, awakening agents, psychoneurotropic agents, neuromuscular blocking agents, antispasmodic agents, antihistaminics, antiallergics, cardiotonics, antiarrhythmics, diuretics, hypotensives, vasopressors, antitussive expectorants, thyroid hormones, sexual hormones, antidiabetics, antitumor agents, antibiotics, chemotherapeutics, and narcotics.

43. The composition of claim 33 wherein the pharmaceutically active ingredients are selected from the group consisting of hypnotics, sedatives, antiepileptics, awakening agents, psychoneurotropic agents, neuromuscular blocking agents, antispasmodic agents, antihistaminics, antiallergics, cardiotonics, antiarrhythmics, diuretics, hypotensives, vasopressors, antitussive expectorants, thyroid hormones, sexual hormones, antidiabetics, antitumor agents, antibiotics, chemotherapeutics, and narcotics.

44. The composition of claim 34 wherein the pharmaceutically active ingredients are selected from the group consisting of hypnotics, sedatives,

antiepileptics, awakening agents, psychoneurotropic agents, neuromuscular blocking agents, antispasmodic agents, antihistaminics, antiallergics, cardiotonics, antiarrhythmics, diuretics, hypotensives, vasopressors, antitussive expectorants, thyroid hormones, sexual hormones, antidiabetics, antitumor agents, antibiotics, chemotherapeutics, and narcotics.

45. The composition of claim 35 wherein the pharmaceutically active ingredients are selected from the group consisting of hypnotics, sedatives, antiepileptics, awakening agents, psychoneurotropic agents, neuromuscular blocking agents, antispasmodic agents, antihistaminics, antiallergics, cardiotonics, antiarrhythmics, diuretics, hypotensives, vasopressors, antitussive expectorants, thyroid hormones, sexual hormones, antidiabetics, antitumor agents, antibiotics, chemotherapeutics, and narcotics.

46. The composition of claim 36 wherein the pharmaceutically active ingredients are selected from the group consisting of hypnotics, sedatives, antiepileptics, awakening agents, psychoneurotropic agents, neuromuscular blocking agents, antispasmodic agents, antihistaminics, antiallergics, cardiotonics, antiarrhythmics, diuretics, hypotensives, vasopressors, antitussive expectorants, thyroid hormones, sexual hormones, antidiabetics, antitumor agents, antibiotics, chemotherapeutics, and narcotics.

47. The composition of claim 32 wherein the substrate comprises cosmetically active ingredients.

48. The composition of claim 34 wherein the substrate comprises cosmetically active ingredients.

49. The composition of claim 34 wherein the substrate comprises cosmetically active ingredients selected from the group consisting of breath freshening compounds, other flavors and fragrances commonly used for oral hygiene and for dental and oral cleansing, tartaric acid, citric acid and vanillin.

50. The composition of claim 32 wherein the substrate comprises nutritional supplements.

51. The composition of claim 34 wherein the substrate comprises nutritional supplements.

52. The composition of claim 32 wherein the coating contains at least one additive selected from the group consisting of cross-linking agents, pharmaceutically active ingredients, cosmetically active ingredients and nutritional supplements.

53. The composition of claim 33 wherein the coating contains at least one additive selected from the group consisting of cross-linking agents, pharmaceutically active ingredients, cosmetically active ingredients and nutritional supplements.

54. The composition of claim 34 wherein the coating contains at least one additive selected from the group consisting of cross-linking agents, pharmaceutically active ingredients, cosmetically active ingredients and nutritional supplements.

55. The composition of claim 35 wherein the coating contains at least one additive selected from the group consisting of cross-linking agents, pharmaceutically active ingredients, cosmetically active ingredients and nutritional supplements.

56. The composition of claim 36 wherein the coating contains at least one additive selected from the group consisting of cross-linking agents, pharmaceutically active ingredients, cosmetically active ingredients and nutritional supplements.

57. A process for coating a substrate comprising (a) preparing an aqueous solution of the composition of claim 1 and (b) applying said solution to the substrate.

58. A process for coating a substrate comprising (a) preparing an aqueous solution of the composition of claim 2 and (b) applying said solution to the substrate.

59. A process for coating a substrate comprising (a) preparing an aqueous solution of the composition of claim 4 and (b) applying said solution to the substrate.

60. A process for coating a substrate comprising (a) preparing an aqueous solution of the composition of claim 17 and (b) applying said solution to the substrate.

61. A process for coating a substrate comprising (a) preparing an aqueous solution of the composition of claim 29 and (b) applying said solution to the substrate.

62. The process of claim 57 wherein the substrate is in a form selected from the group consisting of tablets, granules and beads.

63. The process of claim 58 wherein the substrate is in a form selected from the group consisting of tablets, granules and beads.

64. The process of claim 59 wherein the substrate is in a form selected from the group consisting of tablets, granules and beads.

65. The process of claim 60 wherein the substrate is in a form selected from the group consisting of tablets, granules and beads.

66. The process of claim 63 wherein the aqueous solution contains at least one additive selected from the group consisting of active pharmaceutical ingredients, crosslinking agents, pigments, antioxidants, colorants, opacifying materials, surfactants, stabilizers, silicas, silicones, preservatives, surface treatment agents, flavorants, cosmetically active ingredients, nutritional supplements and other polymers that contribute desired characteristics to the coated substrate.

67. The process of claim 64 wherein the aqueous solution contains at least one additive selected from the group consisting of active pharmaceutical ingredients, crosslinking agents, pigments, antioxidants, colorants, opacifying materials, surfactants, stabilizers, silicas, silicones, preservatives, surface treatment agents,

flavorants, cosmetically active ingredients, nutritional supplements and other polymers that contribute desired characteristics to the coated substrate.

68. The process of claim 66 wherein the additive is selected from the group consisting of polyvalent ion salts.

69. The process of claim 67 wherein the additive is selected from the group consisting of polyvalent ion salts.

70. The process of claim 69 wherein the polyvalent ion salt is selected from the group consisting of aluminum salts, calcium salts, magnesium salts, iron salts, zinc salts, titanium salts and zirconium salts.

71. The process of claim 69 wherein the polyvalent ion salt is selected from the group consisting of aluminum salts and calcium salts.

72. The process of claim 50 wherein aqueous solutions of hydroxypropylcellulose and sodium carboxymethylcellulose are prepared separately and the aqueous solution of hydroxypropylcellulose contains at least one additive selected from the group consisting of active pharmaceutical ingredients, crosslinking agents, pigments, antioxidants, colorants, opacifying materials, surfactants, stabilizers, silicas, silicones, preservatives, surface treatment agents, flavorants, cosmetically active ingredients, nutritional supplements and other polymers that contribute desired characteristics to the coated substrate.

73. The process of claim 72 wherein the additive is selected from the group consisting of polyvalent ion salts.

74. The process of claim 73 wherein the polyvalent ion salt is selected from the group consisting of aluminum salts, calcium salts, magnesium salts, iron salts, zinc salts, titanium salts and zirconium salts.

75. The process of claim 74 wherein the polyvalent ion salt is selected from the group consisting of aluminum salts and calcium salts.

76. The composition of claim 32 wherein the coating comprises at least about 0.5% by weight of the total weight of the composition.

77. The composition of claim 34 wherein the coating comprises at least about 0.5% by weight of the total weight of the composition.

78. The composition of claim 32 wherein the coating comprises up to about 10% by weight of the total weight of the composition.

79. The composition of claim 34 wherein the coating comprises up to about 10% by weight of the total weight of the composition.

80. The composition of claim 35 wherein the coating comprises at least about 0.75% by weight of the total weight of the composition.

81. The composition of claim 35 wherein the coating comprises up to about 2% by weight of the total weight of the composition.

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 A61K9/36 A61K9/62 A61K9/24

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5 080 717 A (YOUNG TENG-SHAU) 14 January 1992 (1992-01-14)	1-10,12, 13, 17-23, 25,26, 29, 32-41, 47,48, 50,51, 57-67
Y	column 1, line 45 - line 50	1-15, 17-41, 47,48, 50,51, 57-67, 76-81
	column 5, line 21 - line 33 example 1; table 1	

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search	Date of mailing of the international search report
19 April 2000	09/05/2000

Name and mailing address of the ISA	Authorized officer
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	FUKUMORI Y, ET AL.: "Computer simulation of agglomeration in the Wurster process" CHEMICAL AND PHARMACEUTICAL BULLETIN, vol. 40, no. 8, 1992, pages 2159-2163, XP002136034 ISSN 0009-2363	1-10,12, 13, 17-23, 25, 32-35, 50,51, 57-60, 62-65
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